IN THE UNITED STATES PATENT AND TRADEMARK OFFICE BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPELLANTS:	Matthias Gerlach *et al.*	**GROUP ART UNIT:**	1623
SERIAL NO.:	10/608,520	**CONFIRMATION NO.:**	
FILING DATE:	June 27, 2003	**EXAMINER:**	Paul V. Ward
TITLE:	Aryl-and Heteroarylcarbonylpiperazines and Their Use for the Treatment of Benign and Malignant Oncoses		

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APPEAL BRIEF

This Appeal Brief is submitted in accordance with 37 C.F.R. § 41.37 in furtherance of the Notice of Appeal filed October 20, 2008, in support of the appeal from the final rejection of claims 1-11, 14-16 and 20 in the above-identified application.

The fee set forth in 37 C.F.R. § 41.20(b)(2) of $540.00 accompanies this Appeal Brief. Appellants believe that no other fees are due. However, the Commissioner is hereby authorized to charge any additional fees that may be due, for further extensions of time or any other purpose associated with this submission, or credit any overpayment, to Appellants' undersigned counsel's deposit account number 06-0923 with reference to docket number 103832-506-NP.

REAL PARTY IN INTEREST

The real party in interest is Zentaris GMBH, the assignee, pursuant to an assignment

recorded in the records of the U.S. Patent and Trademark Office on November 6, 2003 at Reel/Frame 014906/0941 and on December 18, 2003 at Reel/Frame 014906/0291.

RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences pending in the above-identified application that will directly affect or that will be directly affected by the Board's decision in the present appeal.

STATUS OF CLAIMS

The application as filed contained twenty (20) claims. During prosecution, in response to a Restriction Requirement mailed February 23, 2007, Appellants elected Group III in a Response filed March 12, 2007. The Examiner withdrew claims 12-13 and 17-19 from consideration in a non-Final Office Action mailed June 18, 2008. Claims 1-11, 14-16 and 20 are currently being examined.

STATUS OF AMENDMENTS

No amendments to the claims were filed subsequent to the Final Office Action mailed on April 21, 2008.

SUMMARY OF CLAIMED SUBJECT MATTER

The present invention relates to a class of pyrazole-substituted carbonylpiperazines, pharmaceutical compositions for use in the treatment of tumors in humans and in mammals

including the class of pyrazole-substituted carbonylpiperazines, pharmaceutical compositions including the class of pyrazole-substituted carbonylpiperazines, and processes for the production of the pharmaceutical compositions. The claimed pyrazole-substituted carbonylpiperazines include a pyrazole ring which can be substituted with heteroaryl, phenyl, and anthracenyl groups.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues on appeal are (i) whether claims 1-11, 15-16 and 20 are unpatentable under 35 U.S.C. § 103(a) as obvious over Zhu (WO 01/19798 to Zhu *et al.*), (ii) whether claim 14 is unpatentable for failing to comply with 35 U.S.C. §112, ¶ 1; and (iii) whether the amendment to claim 1 as set forth in the Response to Non-Final Office Action filed November 19, 2007 constitutes new matter. The Examiner's grounds for rejections and objection are as follows.

Claims 1-11, 15-16 and 20 are rejected under 35 U.S.C. § 103(a), as being unpatentable over Zhu. The Examiner has alleged that the claimed compounds are a subgenus of the compounds described in Zhu and Zhu describes "very similar subject matter to that claimed" in claim 1, its compositions and uses.

Claim 14 is rejected under 35 U.S.C. § 112, ¶ 1, as failing to comply with the enablement requirement. Examiner has alleged that Appellants have not taught "how to use the compounds of the invention to therapeutic effect for any condition."

The Examiner has alleged that the amendment to claim 1 as set forth in the Response to Non-Final Office Action filed November 19, 2007 with respect to the definition of heteroaryl radical in R_4 constituted new matter.

ARGUMENT

In the ensuing argument, we address each of the Examiner's grounds of rejections and objection pursuant to 37 C.F.R. § 41.67(c)(1)(vii). The grounds of rejections and objection are as follows.

Claims 1-11, 15-16 and 20 are rejected under 35 U.S.C. § 103(a), as being unpatentable over Zhu. Claim 14 is rejected under 35 U.S.C. § 112, ¶ 1, as failing to comply with the enablement requirement. The amendment to claims as set forth in the Amendment filed November 19, 2007 is objected as new matter. For the reasons set forth below, Appellants respectfully traverse each of the grounds.

I. Claims 1-11, 15-16 And 20 Are Nonobvious Over Zhu.

Claims 1-11, 15-16 and 20 are rejected under 35 U.S.C. § 103(a), as being unpatentable over Zhu. Among the rejected claims, each of claims 2-11, 15-16 and 20 recites the compounds of claim 1. Appellants respectfully traverse this rejection as follows.

Claim 1 is directed to a class of pyrazole-substituted carbonylpiperazines, wherein the pyrazole ring can be substituted with heteroaryl, phenyl, and anthracenyl groups, and will be first discussed.

A. The Compounds Of Claim 1 Is Not A Subgenus Of The Genus Disclosed In Zhu.

The Examiner stated in the Final Office Action mailed April 21, 2008 that "Applicant argues that the finding of obviousness is improper because the amended claims are a subgenus." *See* the Final Office Action, page 7.

However, the Response to Non-Final Office Action dated November 19, 2007 clearly stated that "the compounds of amended claim 1 are ***not*** a subgenus of the genus disclosed in Zhu

et al." (emphasis in original). Claim 1 is directed to a class of pyrazole-substituted carbonylpiperazines, wherein the pyrazole ring can be substituted with heteroaryl, phenyl, and anthracenyl groups, while in the genus disclosed in Zhu, the substitute (X) on a heteroaryl (G, *e.g.*, pyrazole) cannot be an anthracenyl group. Therefore, the compounds of claim 1 are ***not*** a subgenus of the genus disclosed in Zhu.

B. The Compounds Disclosed In Zhu Have A Different Utility

The Examiner asserted in the Final Office Action mailed April 21, 2008 that "Zhu describes very similar subject matter to that claimed herein directed to amended claim 1, its compositions and uses." *See* the Final Office Action, page 7.

The compounds disclosed in Zhu are useful for treating or preventing coagulation disorders, while the compounds of claim 1 have the properties of treating tumors. *In re Albrecht*, 514 F.2d 1389, 1392 (CCPA 1975) ("the prior art compound so irritated the skin that it could not be regarded as useful for the disclosed anesthetic purpose, and therefore a person skilled in the art would not have been motivated to make related compounds."). Accordingly, Zhu would not provide any motivation to one of ordinary skill in the art, in order to preparing anti-tumor compounds, to modify the compounds disclosed in Zhu and arrive at the compounds of claim 1.

C. The Compounds Of Claim 1 Are Nonobvious Over Zhu

The Examiner further asserted in the Final Office Action mailed April 21, 2008 that "[a] prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within a genus." *See* the Final Office Action, page 7.

However, the fact that a claimed species is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382

(Fed. Cir. 1994)("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."). In this regard, Manual of Patent Examining Procedure ("M.P.E.P.") § 2144.08.II.A.4 instructs Office personnel should (a) consider the size of the genus; (b) consider the express teachings; (c) consider the teachings of structural similarity; (d) consider the teachings of similar properties; (e) consider the predictability of the technology; and (f) consider any other teaching to support the selection of the species or subgenus.

First, in the present case, the size of the genus disclosed in Zhu is extremely large. Zhu discloses a genus having the formula:

A-Q-D-E-G-J-X

Wherein:

A is selected from:

(a) C_1-C_6-alkyl;

(b) C_3-C_8-cycloalkyl;

(c) $-N(R^2,R^3)$, $-C(=NR^2)-R^3$, $-C(=NR^2)N(R^2,R^3)$, $-N(R^3)-C(=NR^2)N(R^2, R^3)$-, and $-N(R^2)C(=NR^3)-R^2$

(d) phenyl, which is independently substituted with 0-2 R^1 substituents;

(e) naphthyl, which is independently substituted with 0-2 R^1 substituents; and

(f) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^1 substituents;

Q is selected from the group consisting of:

a direct link, divalent -C_{1-4}alkyl, divalent -C_{2-4}alkenyl, divalent -C_{2-4}alkynyl, -C(=O)-, -C(=NH)-, -C(=NMe)-, -N(-R^4)-, -N(-R^4)-CH_2-, -C(=O)-N(-R^4)-, -N(-R^4)-C(=O)-, -S(=O)$_2$-, -O-, -S(=O)$_2$-N(-R^4)- and –N(-R^4)-S(=O)$_2$-, wherein one or more hydrogens on each of the divalent C_{1-4}alkyl, divalent C_{2-4}alkenyl and divalent C_{2-4}alkynyl moieties can be replaced with a -R^4 group;

D is selected from the group consisting of:

(a) a direct link;

(b) phenyl, which is independently substituted with 0-2 R^{1a} substituents;

(c) naphthyl, which is independently substituted with 0-2 R^{1a} substituents; and

(d) monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be subsituted from 0-2 R^{1a} substituents;

E is selected from the group consisting of:

a direct link, -$(CH_2)_q$-C(=O)-, -$(CH_2)_q$-N(-R^5)-C(=O)-$(CH_2)_x$-, -$(CH_2)_q$-C(=O)-N(-R^5)-$(CH_2)_x$-, -$(CH_2)_q$-N(-R^5)-$(CH_2)_x$-, , -$(CH_2)_q$-N(R^5)CO-$NR^6(CH_2)_x$ and -SO_2-;

G is selected from the group consisting of:

phenyl, which is substituted with 0-2 R^{1b} groups; and

a 5-6 membered aromatic and non-aromatic heterocyclic ring containing 1-4 hetero atoms selected from N, O and S wherein the heterocyclic ring is substituted with 0-2 R^{1b} groups;

J is selected from the group consisting of:

a direct link, -S(=O)$_2$-, -C(=O)-, -N(-R^7)-S(=O)$_2$-, -C(=O)-N(-R^7)-S(=O)$_2$-, -C(=O)-N(-R^7)-$(CH_2)_y$-, -S(=O)$_2$-N(-R^7) -$(CH_2)_y$-, and -N(-R^7)-C(=O)-$(CH_2)_y$-;

X is selected from the group consisting of:

phenyl, which is substituted with 0-3 R^{1c} groups;

naphthyl, which is substituted with 0-3 R^{1c} groups;

a 6-membered heteroaromatic ring containing from 1-2 nitrogen atoms, wherein the ring is substituted with 0-3 R^{1c} groups; and

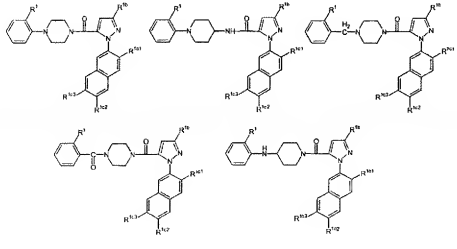
a fused heterobicyclic ring system, wherein the ring system contains 1-3 heteroatoms selected from N, O and S and is substituted with 0-3 R^{1c} groups;

See claim 1 in Zhu.

Second, Zhu fails to teach which of the possibilities corresponds to the claimed pyrazole-substituted carbonylpiperazines of claim 1.

Third, Zhu does not specify similar compounds to those claimed pyrazole-substituted carbonylpiperazines of claim 1. At most , Zhu discloses 53 Tables of subgenera, one of the Tables describes the following:

Table 8



Id. at page 39. The compounds disclosed in the other 52 Tables do not even have piperazines at the cores.

Fourth, as set forth above, the compounds disclosed in Zhu are useful for treating or preventing coagulation disorders, while the compounds of claim 1 have the properties of treating tumors.

Accordingly, one of ordinary skill in the art, without any teaching or suggestion, would have not expected that any species in such a size of the Zhu's genus would have similar properties, and therefore would have not been able to modify the species to arrive at pyrazole-substituted carbonylpiperazines as claimed in claim 1 for further studies.

Accordingly, the Examiner has not met his burden of establishing a *prima facie* case of obviousness.

In addition, the specification provides that it has surprisingly found that novel compounds of the invention are suitable for the treatment of benign and malignant tumors (*see* paragraph [0010]), and that the *in vitro* testing results show a very potent inhibition of the proliferation of selected tumor cell lines (*see* paragraph [0146]). Therefore, even a *prima facie* case of obviousness had been established by the Examiner, it can be rebutted by the unexpected findings provided in the specification.

For the reasons set forth above, there is neither any disclosure nor any suggestion in Zhu that would have rendered claim 1 obvious. By the same token, claims 2-11, 15-16 and 20, which include all of the limitations of claim 1, are also not rendered obvious by Zhu.

Appellants accordingly request that the rejection of claims 1-11, 15-16 and 20 under 35 U.S.C. § 103 be withdrawn.

II. Claim 14 Is Enabled.

Claim 14 is rejected under 35 U.S.C. § 112, ¶ 1, as failing to comply with the enablement requirement. Claim 14 is directed to a pharmaceutical composition for use in the treatment of tumors containing at lest one compound of the general formula (1) as claimed in claim 1. The Examiner alleged in the Final Office Action mailed April 21, 2008 that "[t]he term 'pharmaceutical composition' specifies that at least some therapeutic benefit arise from some property of the composition. However, Applicant has not taught how to use the compounds of the invention to therapeutic effect for ***any condition***" (emphasis added). *See* the Final Office Action, page 3. Further, the Examiner asserted that

> A great deal of experimentation is required. In order for there to be a method of treating tumor/cancer generally, ***as claimed by the applicant***, it would be necessary to show that a vast range of different types of tumors/cancers can be treated that have differing cell types, locations and potentials for metastases . . . one of ordinary skill in the art would require a significant amount of experimentation in order to determine the effective dosage to treat the multitudes of different types of tumor/cancer with the claimed compound individually or in combination with other therapeutic agents. Thus, it can be safely concluded that the instant case fails to provide an enabling disclosure for the treatment of tumor/cancer.

Id. at page 6 (emphasis added). Appellants respectfully disagree.

First, Appellants would like to point out that claim 14 is directed to a pharmaceutical composition, not to a method of treatment, as alleged by the Examiner.

With respect to non-enablement, M.P.E.P. § 2164.4 states: "[i]n order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." Also *see In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of the

protection provided by a claim is not adequately enabled by the disclosure). However, the Examiner has not provided a reasonable explanation as to why the specification fails to teach one of skill in the art to use the compounds of the invention "for ***any condition***." Further, given the experimental data provided in the specification, *i.e.*, Example 18 (*in vitro* testing the compounds of the invention[1] for inhibition of the proliferation of various tumor cell lines) and Example 19 (*in vitro* testing the compounds of the invention for inhibition of the polymerization of tubulin), the specification at least teaches one of ordinary skill in the art to use the compounds of the invention to inhibit tumor cell lines or inhibit tubulin polymerization. Therefore, the Examiner has not met his initial burden to establish a reasonable basis to question the enablement provided for the claimed invention.

Moreover, Appellants would like to point out that as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of Section 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970). Here, Appellants not only provide general guidance on the use of the compounds of the invention for the treatment of benign and malignant tumors (*see* paragraphs [0003] and [0065]-[0067]), but also present specific examples for *in vitro* testing the compounds of the invention for inhibition of the proliferation of various tumor cell lines (*see* Example 18) and for *in vitro* testing the compounds of the invention for inhibition of the polymerization of tubulin (*see* Example 19).

In addition, additional data was submitted to the Examiner on November 19, 2007, together with the Response to Non-Final Office Action. The additional data includes *in vitro*

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[1] Compounds 14-16 are pyrazole compounds elected for examination.

data on selective tumor models. The tested compounds include 13 compounds that fall within the scope of the general formula (I) as recited in claim 1, representing compounds in which R_1 is 9H-fluorene, 9H-xanthene, and 1H-pyrazole. For each compound, assays were conducted with 3.16 μg/mL of tested compound to determine antiproliferative activities (% inhibition) in the tumor cell lines: KB/HELA, SKOV-3, SF-268, NCI-H460 and RKOp27. The assay of inhibiting tumor cell lines is described in the specification, Example 18. Moreover, for each compound, the EC_{50} values against the just-mentioned cell lines were also determined. In addition, the metabolic stability by means of liver microsomes was determined for 3 compounds of claim 1. *See* Appendix A. "An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention." *See* M.P.E.P. §2164.02. Thus, one person skilled in the art, provided with the general guidance and specific examples in the specification directed against a variety of tumors, would have a reasonable expectation that a pharmaceutical composition containing the compounds of the invention would have efficacy in a variety of abnormal tumorous disorders. Moreover, when the artisan is fully able to utilize claimed subject matter as described in the specification, clinical testing should not be made a prerequisite to patentability. *See In re Hartop*, 311 F.2d 249 (CCPA 1962) and *Ex parte Rubin*, 5 USPQ 2d 1461 (BPAI 1987).

For at least the foregoing reasons, Appellants submit claim 14 is enabled.

III. The Amendment To Claim 1 Does Not Introduce Any New Matter.

The Examiner objected to the amendment to claim 1 with respect to the definition of heteroaryl radical in R_1 as set forth in the Response to Non-Final Office Action filed November 19, 2007 and alleged the amendment constitutes new matter. Appellants would like to bring the

Examiner's attention to original filed claim 5, which includes the definition of heteroaryl radical. Thus, the definition of heteroaryl radical was present in the specification at the time this application was filed. Accordingly, the amendment to claim 1 does not introduce any new matter.

CONCLUSION

In view of the arguments above, Appellants respectfully submit that claims 1-11, 14-16 and 20 are patentable and urges the Board of Patent Appeals and Interferences to reverse all of the Examiner's rejections and objection as to each of these claims.

Respectfully submitted,

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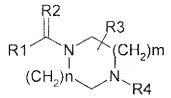
CLAIMS APPENDIX

Listing of Claims

1. (Previously Presented) An aryl- or heteroaryl-substituted piperazinylcarbonyl compound of the general formula (1),



1

wherein:

R_1: 1H-pyrazole,

where the bonding can take place via any desired and possible ring member of the heteroaryl or aryl radical and the aromatics and heteroaromatics can be mono- or polysubstituted or unsubstituted, wherein the aryl radical is selected from the group consisting of phenyls and anthracenyls;

R_2: O, S;

R_3: represents one or up to 16 substituents selected from the group: H, unsubstituted or substituted alkyl, halogen, COOH, $CONH_2$, where the substituents can be arranged vicinally or geminally on the heterocycle;

R_4: unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted alkylaryl, unsubstituted or substituted alkylhetaryl, wherein the heteroaryl radical can be pyrrolyl, furyl, thienyl, thiazolyl, triazolyl, tetrazolyl, oxazolyl, isothiazolyl, isoxazolyl, pyrazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, benzothiazolyl, indolyl,

indolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, carbazolyl, phenazinyl, phenothiazinyl, purinyl, acridinyl, phenanthrinyl;

m: 0-3; and

n: 1;

or a physiologically salt, or hydrate thereof.

2. (Previously Presented) An aryl- or heteroarylcarbonylpiperazine compound of the general formula (I) as claimed in claim 1, in which

halogen comprises the halogen atoms fluorine, chlorine, bromine and iodine,

metal comprises metal ions selected from the group consisting of sodium, potassium, lithium, magnesium, calcium, zinc and manganese ions,

alkyl comprises acyclic saturated or unsaturated hydrocarbon radicals, having 1 to 20 C atoms, which can be branched or straight-chain and unsubstituted or mono- or polysubstituted, alkenyls having at least one C-C double bond and alkynyls at least one C-C triple bond,

cycloalkyl comprises cyclic hydrocarbons having 3-12 carbon atoms, which can be saturated or unsaturated, unsubstituted or substituted, whose binding to the compounds of the general formula (I) can take place via any desired and possible ring member of the cycloalkyl radical and the cycloalkyl radical can also be part of a bi- or polycyclic system.

heterocyclyl stands for a 3-, 4-, 5-, 6-, 7- or 8-membered cyclic organic radical, which is unsubstituted or mono- or polysubstituted, saturated or unsaturated, but not aromatic, which contains at least 1, optionally 2, 3, 4 or 5 heteroatoms, preferably nitrogen, oxygen and sulfur, where the heteroatoms are identical or different and whose bonding to the compounds of the general formula (1) can take place via any desired and possible ring member of the heterocyclyl radical, where the heterocycle can also be part of a bi- or polycyclic system,

aryl denotes aromatic hydrocarbons, which are unsubstituted or mono- or polysubstituted, inter alia phenyls, naphthyls and anthracenyls, whose radicals can also be fused to further saturated, (partially) unsaturated or aromatic ring systems and whose bonding to the compounds of the general formula (1) can take place via any desired and possible ring member of the aryl radical,

heteroaryl stands for a 5-, 6- or 7-membered cyclic aromatic radical, which is unsubstituted or mono- or polysubstituted, identically or differently, which contains at least 1, optionally also 2, 3, 4 or 5 heteroatoms, preferably nitrogen, oxygen and sulfur, where the heteroatoms are identical or different and whose bonding to the compounds of the general formula (1) can take place via any desired and possible ring member of the heteroaryl radical, where the heterocycle can also be part of a bi- or polycyclic system,

alkylcycloalkyl, alkylheterocyclyl, alkylaryl or alkylheteroaryl have the meanings defined for alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl and the cycloalkyl, heterocyclyl, aryl or

heteroaryl radical is bonded to the compounds of the general formula (1) via a C1-8 –alkyl group,

substituted in connection with alkyl, alkenyl and alkynyl can denote the substitution of a hydrogen radical by F, Cl, Br, I, CN, NH_2, NH-alkyl, NH-cycloalkyl, NH-aryl, NH-heteroaryl, NH-alkylaryl, NH-alkylheteroaryl, NH-heterocyclyl, NH-alkyl-OH, $N(alkyl)_2$, $N(alkylaryl)_2$, $N(alkylheteroaryl)_2$, $N(heterocyclyl)_2$, $N(alkyl\text{-}OH)_2$, NO, NO_2, SH, S-alkyl, S-cycloalkyl, S-aryl, S-heteroaryl, S-alkylaryl, S-alkylheteroaryl, S-heterocyclyl, S-alkyl-OH, S-alkyl-SH, S-alkyl, S-S-cycloalkyl, S-S-aryl, S-S-heteroaryl, S-S-alkylaryl, S-S-alkylheteroaryl, S-S-heterocyclyl, SS-alkyl-OH, S-S-alkyl-SH, S-S-alkyl-C(O)-NH-heterocyclyl, OH, O-alkyl, O-cycloalkyl, O-alkylcycloalkyl, O-aryl, O-heteroaryl, O-alkylaryl, O-alkylheteroaryl, O-heterocyclyl, O-alkylheterocyclyl, O-alkyl-OH, O-alkyl-O-alkyl, $O\text{-}SO_2\text{-}N(alkyl)_2$, $O\text{-}SO_2\text{-}OH$, $O\text{-}SO_2\text{-}O\text{-}alkyl$, $O\text{-}SO_2\text{-}O\text{-}cycloalkyl$, $O\text{-}SO_2\text{-}O\text{-}heterocycloalkyl$, $O\text{-}SO_2\text{-}O\text{-}alkylcycloalkyl$, $O\text{-}SO_2\text{-}O\text{-}alkylheterocycloalkyl$, $O\text{-}SO_2\text{-}O\text{-}aryl$, $O\text{-}SO_2\text{-}O\text{-}heteroaryl$, $O\text{-}SO_2\text{-}O\text{-}alkylaryl$, $O\text{-}SO_2\text{-}O\text{-}alkylheteroaryl$, $O\text{-}SO_2\text{-}alkyl$, $O\text{-}SO_2\text{-}cycloalkyl$, $O\text{-}SO_2\text{-}heterocycloalkyl$, $O\text{-}SO_2\text{-}alkylcycloalkyl$, $O\text{-}SO_2\text{-}alkylheterocycloalkyl$, $O\text{-}SO_2\text{-}aryl$, $O\text{-}SO_2\text{-}heteroaryl$, $O\text{-}SO_2\text{-}alkylaryl$, $O\text{-}SO_2\text{-}alkylheteroaryl$, O-C(O)-alkyl, O-C(O)-cycloalkyl, O-C(O)-heterocycloalkyl, O-C(O)-alkylcycloalkyl, O-C(O)-alkylheterocycloalkyl, O-C(O)-aryl, O-C(O)-heteroaryl, O-C(O)-alkylaryl, O-C(O)-alkylheteroaryl, O-C(O)O-alkyl, O-C(O)O-cycloalkyl, O-C(O)O-heterocycloalkyl, O-C(O)O-alkylcycloalkyl, O-C(O)O-alkylheterocycloalkyl, O-C(O)O-aryl, O-C(O)O-heteroaryl, O-C(O)O-alkylaryl, O-C(O)O-alkylheteroaryl, O-C(O)NH-alkyl, O-C(O)NH-cycloalkyl, O-C(O)NH-heterocycloalkyl, O-C(O)NH-alkylcycloalkyl, O-C(O)NH-

alkylheterocycloalkyl, O-C(O)NH-aryl, O-C(O)NH-heteroaryl, O-C(O)NH-alkylaryl, O-C(O)NH-alkylheteroaryl, O-C(O)N(alkyl)$_2$, O-C(O)N(cycloalkyl)$_2$, O-C(O)N(heterocycloalkyl)$_2$, O-C(O)N(alkylcycloalkyl)$_2$, O-C(O)N(alkylheterocycloalkyl)$_2$, O-C(O)N(aryl)$_2$, O-C(O)N(heteroaryl)$_2$, O-C(O)N(alkylaryl)$_2$, O-C(O)N(alkylheteroaryl)$_2$, O-P(O)(OH)$_2$, O-P(O)(O-metal)$_2$, O-P(O)(O-alkyl)$_2$, O-P(O)(O-cycloalkyl)$_2$, O-P(O)(O-aryl)$_2$, O-P(O)(O-heteroaryl)$_2$, O-P(O)(O-alkylaryl)$_2$, O-P(O)(O-alkylheteroaryl)$_2$,O-P(O)(N-alkyl)$_2$(N-alkyl)$_2$,O-P(O)(N-cycloalkyl)$_2$(N-cycloalkyl)$_2$,O-P(O)(N-heterocycloalkyl)$_2$(N-heterocycloalkyl)$_2$, O-P(O)(N-aryl)$_2$(N-aryl)$_2$, O-P(O)(N-heteroaryl)$_2$(N-heteroaryl)$_2$, O-P(O)(N-alkylaryl)$_2$(N-alkylaryl)$_2$, O-P(O)(N-alkylheteroaryl)$_2$(N-alkylheteroaryl)$_2$, CHO, C(O)-alkyl, C(S)-alkyl, C(O)-aryl, C(S)-aryl, C(O)-alkylaryl, C(S)-alkylaryl, C(O)-heterocyclyl, C(O)-heteroaryl, C(O)-alkylheteroaryl, C(S)-heterocyclyl, CO_2H, CO_2-alkyl, CO_2-cyclyl, CO_2-heterocyclyl, CO_2-aryl, CO_2-heteroaryl, CO_2-alkylaryl, C(O)-NH_2, C(O)NH-alkyl, C(O)NH-aryl, C(O)NH-heterocyclyl, C(O)NH-alkylheterocyclyl, C(O)N(alkyl)$_2$, C(O)N(alkylaryl)$_2$, C(O)N(alkylheteroaryl)$_2$, C(O)N(heterocyclyl)$_2$, SO-alkyl, SO_2-alkyl, SO_2-aryl, SO_2-alkylaryl, SO_2-heteroaryl, SO_2-alkylheteroaryl, SO_2NH_2, SO_3H, CF_3, CHO, CHS, alkyl, cycloalkyl, aryl, alkylaryl, heteroaryl, alkylheterocyclyl and/or heterocyclyl, where in the case of polysubstituted radicals these can be polysubstituted either on different or on identical atoms and the polysubstitution can take place with the same or different substituents,

substituted in connection with aryl, heterocyclyl, heteroaryl, alkylaryl and cycloalkyl can mean the substitution of one or more hydrogen atoms of the ring system by F, Cl, Br, I, CN, NH_2, NH-alkyl, NH-aryl, NH-heteroaryl, NH-alkylaryl, NH-alkylheteroaryl, NH-heterocyclyl, NH-alkyl-

OH, N(alkyl)$_2$, NC(O)alkyl, N(alkylaryl)$_2$, N(alkylheteroaryl)$_2$, N(heterocyclyl)$_2$, N(alkyl-OH)$_2$, NO, NO$_2$, SH, S-alkyl, S-aryl, S-heteroaryl, S-alkylaryl, S-alkylheteroaryl, S-heterocyclyl, S-alkyl-OH, S-alkyl-SH, OH, O-alkyl, O-cycloalkyl, O-alkylcycloalkyl, O-aryl, O-heteroaryl, O-alkylaryl, O-alkylheteroaryl, O-heterocyclyl, O-alkylheterocyclyl, O-alkyl-OH, O-alkyl-O-alkyl, O-SO$_2$-N(alkyl)$_2$, O-SO$_2$-OH, O-SO$_2$-O-alkyl, O-SO$_2$-O-cycloalkyl, O-SO$_2$-O-heterocycloalkyl, O-SO$_2$-O-alkylcycloalkyl, O-SO$_2$-O-alkylheterocycloalkyl, O-SO$_2$-O-aryl, O-SO$_2$-O-heteroaryl, O-SO$_2$-O-alkylaryl, O-SO$_2$-O-alkylheteroaryl, O-SO$_2$-alkyl, O-SO$_2$-cycloalkyl, O-SO$_2$-heterocycloalkyl, O-SO$_2$-alkylcycloalkyl, O-SO$_2$-alkylheterocycloalkyl, O-SO$_2$-aryl, O-SO$_2$-heteroaryl, O-SO$_2$-alkylaryl, O-SO$_2$-alkylheteroaryl, O-C(O)-alkyl, O-C(O)-cycloalkyl, O-C(O)-heterocycloalkyl, O-C(O)-alkylcycloalkyl, O-C(O)-alkylheterocycloalkyl, O-C(O)-aryl, O-C(O)-heteroaryl, O-C(O)-alkylaryl, O-C(O)-alkylheteroaryl, O-C(O)O-alkyl, O-C(O)O-cycloalkyl, O-C(O)O-heterocycloalkyl, O-C(O)O-alkylcycloalkyl, O-C(O)O-alkylheterocycloalkyl, O-C(O)O-aryl, O-C(O)O-heteroaryl, O-C(O)O-alkylaryl, O-C(O)O-alkylheteroaryl, O-C(O)NH-alkyl, O-C(O)NH-cycloalkyl, O-C(O)NH-heterocycloalkyl, O-C(O)NH-alkylcycloalkyl, O-C(O)NH-alkylheterocycloalkyl, O-C(O)NH-aryl, O-C(O)NH-heteroaryl, O-C(O)NH-alkylaryl, O-C(O)NH-alkylheteroaryl, O-C(O)N(alkyl)$_2$, O-C(O)N(cycloalkyl)$_2$, O-C(O)N(heterocycloalkyl)$_2$, O-C(O)N(alkylcycloalkyl)$_2$, O-C(O)N(alkylheterocycloalkyl)$_2$, O-C(O)N(aryl)$_2$, O-C(O)N(heteroaryl)$_2$, O-C(O)N(alkylaryl)$_2$, O-C(O)N(alkylheteroaryl)$_2$, O-P(O)(OH)$_2$, O-P(O)(O-metal)$_2$, O-P(O)(O-alkyl)$_2$, O-P(O)(O-cycloalkyl)$_2$, O-P(O)(O-aryl)$_2$, O-P(O)(O-heteroaryl)$_2$, O-P(O)(O-alkylaryl)$_2$, O-P(O)(O-alkylheteroaryl)$_2$, O-P(O)(N-alkyl)$_2$(N-alkyl)$_2$,O-P(O)(N-cycloalkyl)$_2$(N-cycloalkyl)$_2$,O-P(O)(N-heterocycloalkyl)$_2$(N-heterocycloalkyl)$_2$, O-P(O)(N-aryl)$_2$(N-aryl)$_2$, O-P(O)(N-heteroaryl)$_2$(N-heteroaryl)$_2$, O-P(O)(N-alkylaryl)$_2$(N-alkylaryl)$_2$, O-

P(O)(N-alkylheteroaryl)$_2$(N-alkylheteroaryl)$_2$, CHO, C(O)-alkyl, C(S)-alkyl, C(O)-aryl, C(S)-aryl, C(O)-alkylaryl, C(S)-alkylaryl, C(O)-heterocyclyl, C(S)-heterocyclyl, CO_2H, CO_2-alkyl, CO_2-alkylaryl, C(O)-NH_2, C(O)NH-alkyl, C(O)NH-aryl, C(O)NH-heterocyclyl, C(O)N(alkyl)$_2$, C(O)N(alkylaryl)$_2$, C(O)N(alkylheteroaryl)$_2$, C(O)N(heterocyclyl)$_2$, SO-alkyl, SO_2-alkyl, SO_2-aryl, SO_2-alkylaryl, SO_2-heteroaryl, SO_2-alkylheteroaryl, SO_2NH_2, SO_3H, CF_3, CHO, CHS, alkyl, cycloalkyl, aryl, alkylaryl, heteroaryl, alkylheterocyclyl and/or heterocyclyl, where the substituents are identical or different and can occur in any desired and possible position of the aryl, heterocyclyl, heteroaryl, alkylaryl and cycloalkyl radical and where polysubstituted radicals can be polysubstituted with the same or with different substituents, either on different or on identical atoms.

3. (Previously Presented) An aryl- or heteroarylcarbonylpiperazine compound of the general formula (1) as claimed in claim 1, wherein the alkyl radical can be methyl, ethyl, n-propyl, 2-propyl, n-butyl, sec.-butyl, tert.-butyl, n-pentyl, iso-pentyl, neo-pentyl, n-hexyl, 2-hexyl, n-octyl, ethylenyl (vinyl), ethynyl, propenyl (-CH_2CH=CH_2; -CH=CH-CH_3, -C(=CH_2)-CH_3), propynyl (-CH_2-C≡CH, -C≡C-CH_3), butenyl, butynyl, pentenyl, pentynyl, hexenyl, hexynyl, octenyl and octynyl.

4. (Previously Presented) An aryl- or heteroarylcarbonylpiperazine compound of the general formula (1) as claimed in claim 2, wherein the heterocyclyl radical can be tetrahydrofuryl, tetrahydropyranyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl.

5. (Previously Presented) An aryl- or heteroarylcarbonylpiperazine compound of the general formula (1) as claimed in claim 1, wherein the heteroaryl radical can be pyrrolyl, furyl, thienyl, thiazolyl, triazolyl, tetrazolyl, oxazolyl, isothiazolyl, isoxazolyl, pyrazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, benzothiazolyl, indolyl, indolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, carbazolyl, phenazinyl, phenothiazinyl, purinyl, acridinyl, phenanthrinyl.

6. (Original) A compound of the general formula (1) as claimed in claim 1, wherein R_4 stands for phenyl, which is unsubstituted or substituted by one to five identical or different (C_1-C_6)-alkoxy groups, where adjacent oxygen atoms can also be linked by (C_1-C_2)-alkylene groups.

7. (Original) A compound of the general formula (1) as claimed in claim 1, wherein R_4 stands for 3,5-dimethoxyphenyl.

8. (Previously Presented) A compound of the general formula (1) as claimed in claim 1, wherein R_4 stands for 3-methoxyphenyl.

9. (Previously Presented) A compound of the general formula (1) as claimed in claim 1, wherein the physiologically salt of the compound of the general formula (1) is formed by neutralization of the basic compounds with inorganic and organic acids or neutralization of the acidic compounds with inorganic and organic bases.

10. (Original) An aryl- or heteroarylcarbonylpiperazine compound of the general formula (1) as claimed in claim 1, having at least one asymmetric carbon atom, in the form of its racemates, in the form of the pure enantiomers and/or diastereomers or in the form of mixtures of these enantiomers and/or diastereomers or in the form of the tautomers.

11. (Previously Presented) A compound of the general formula (1) as claimed in claim 1, which is one of the following compounds:

4-[4-(3,5-Dimethoxyphenyl)piperazine-1-carbonyl]fluoren-9-one (**1**)

4-[4-(6-methylpyridin-2-yl)piperazine-1-carbonyl]fluoren-9-one (**2**)

4-[4-(3-Hydroxyphenyl)piperazine-1-carbonyl]fluoren-9-one (**3**)

[4-(3,5-Dimethoxyphenyl)piperazin-1-yl]-(5-methyl-3-phenylisoxazol-4-yl)methanone (**4**)

cinnolin-4-yl-[4-(3,5-dimethylphenyl)piperazin-1-yl]methanone (**5**)

cinnolin-4-yl-[4-(6-methylpyridin-2-yl)piperazin-1-yl]methanone (**6**)

(3,5-Bis-methylsulfanylisothiazol-4-yl)-[4-(6-methylpyridin-2-yl)piperazin-1-yl]methanone (**7**)

[4-(3,5-Dimethoxyphenyl)piperazin-1-yl]-isoquinolin-1-ylmethanone (**8**)

[4-(3,5-Dimethoxyphenyl)piperazin-1-yl]-(9H-fluoren-1-yl)methanone (**9**)

(9H-Fluoren-9-yl)-[4-(3-methoxyphenyl)piperazin-1-yl]methanone (**10**)

(9H-Fluoren-1-yl)-[4-(3-methoxyphenyl)piperazin-1-yl]methanone (**11**)

[4-(3,5-Dimethoxyphenyl)piperazin-1-yl]-(9H-xanthen-9-yl)methanone (**12**)

[4-(3-methoxyphenyl)piperazin-1-yl]-(9H-xanthen-9-yl)methanone (**13**)

[4-(3-methoxyphenyl)piperazin-1-yl]-(2-phenyl-2H-pyrazol-3-yl)methanone (**14**)

[4-(6-methylpyridin-2-yl)piperazin-1-yl]-(2-phenyl-2H-pyrazol-3-yl)methanone (**15**)

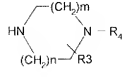
[4-(3-Hydroxyphenyl)piperazin-1-yl]-(2-phenyl-2H-pyrazol-3-yl)methanone (**16**)

[4-(3,5-Dimethoxyphenyl)piperazin-1-yl]-[1-(4-nitrophenyl)-5-trifluoromethyl-1H-pyrazol-4-yl]methanone (**17**).

12. (Withdrawn) A process for the preparation of the aryl- and heteroarylcarbonylpiperazine compounds as claimed in one of claims 1, which comprises reacting a carboxylic acid of the general formula 2, in which R_1 and R_2 have the meanings as defined in claim 1 and Y stands for a leaving group,

R1: aryl, heteroaryl

Formula 2



Formula 3

with an amine of the general formula 3, in which R_4, m and n have the meanings as defined in claim 1, optionally using a condensing agent and/or catalyst and diluents and auxiliaries with formation of the desired products.

13. (Withdrawn) A method for the treatment of tumors in humans and in mammals, comprising administering an aryl- and heteroarylcarbonylpiperazine compounds of the general formula (1) as claimed in claim 1 to a human or mammal in need of the treatment.

14. (Original) A pharmaceutical composition for use in the treatment of tumors in humans and in mammals, comprising at least one compound of the general formula (1) as claimed in claim 1.

15. (Previously Presented) A pharmaceutical composition, comprising one or more compounds of the general formula (1) as claimed in claim 1 in and physiologically excipient, additive and/or vehicle.

16. (Previously Presented) A process for the production of a pharmaceutical composition as claimed in claim 15, which comprises processing one or more aryl- and heteroarylcarbonylpiperazine compounds of the general formula (1) as claimed in claim 1 with a physiologically excipient, additive and/or vehicle to give a pharmaceutical preparation, or bringing them into a therapeutically administrable form.

17. (Withdrawn) A process for the treatment of benign and malignant tumors in humans and mammals, which comprises administering at least one compound of the general formula (1) as claimed in claim 1 to a human or mammal at a dose effective for tumor treatment.

18. (Withdrawn) The process as claimed in claim 12, wherein Y is halogen, hydroxyl, (C_1-C_6)-alkoxy, -O-tosyl, -O-mesyl, tetrazolyl or imidazolyl.

19. (Withdrawn) The process as claimed in claim 18, wherein Y is methoxy or ethoxy.

20. (Previously Presented) The pharmaceutical composition as claimed in claim 14, further comprising a pharmaceutically excipient, additive and/or vehicle.

EVIDENCE APPENDIX

A Copy of Zhu discussed herein, having been cited by the Examiner, is available in the prosecution history. A copy of additional data on selective tumor models referred to in this Appeal Brief is attached hereto as Evidence Appendix 1.

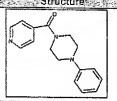
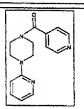
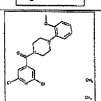
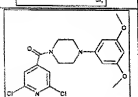
It is believed that there is no other evidence submitted pursuant to 37 C.F.R. §§ 1.130, 1.131 or 1.132 or any other evidence entered by the Examiner and relied upon by Appellants in this appeal.

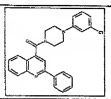
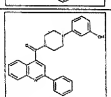
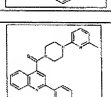
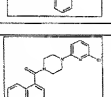
Evidence Appendix 1: additional data on selective tumor models

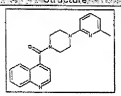
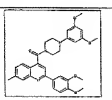
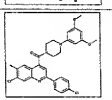
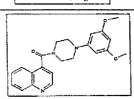
RELATED PROCEEDINGS APPENDIX

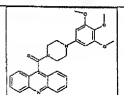
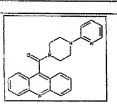
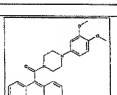
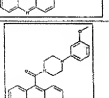
NONE

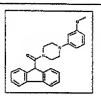
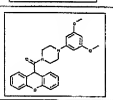
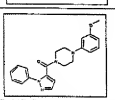
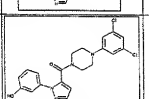
APPENDIX A

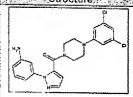
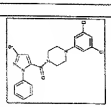
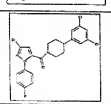
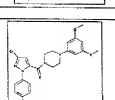
D-No.	Corporate ID	Structure	Patent	KB/HELA	SKOV-3	SF-268	NCI-H460	RKOp27	KB/HELA	SKOV-3	SF-268	NCI-H460	RKOp27	RKOp27 Induced
				%INH (3.16ug/ml)					EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]
D-36138	S40390		D1: 00/13PH	-5,6	-2,9	-5,3	7,4	nd	Biorep >3.16	Biorep >3.16	nd	nd	nd	nd
D-32848	S37100		D1: 00/13PH	-16,5	-7,6	2,4	11,6	8,4	Biorep >3.16	Biorep >3.16	nd	nd	nd	nd
D-21419	S25700		D1: 00/13PH	nd	nd	nd	nd	nd	>3.16	>3.16	>3.16	>3.16	>3.16	>3.16
D-21432	S25713		D1: 00/13PH	nd	nd	nd	nd	nd	0,996	0,415	0,898	0,633	0,390	>3.16

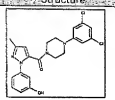
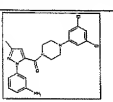
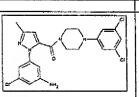
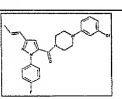
ID-No.	Corporate ID	Structure	Patent	KB/HELA	SKOV-3	SF-268	NCI-H460	RKOp27	KB/HELA	SKOV-3	SF-268	NCI-H460	RKOp27	RKOp27 Induced
				%INH [3.16ug/ml]					EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]
D-87196	S107791		D2: 00/14PH	63,1	62,3	57,9	77,1	85,5	>3.16	>3.16	>3.16	10,020	2,096	>3.16
D-87135	S107728		D2: 00/14PH	51,7	63,4	43,7	73,3	94,6	>3.16	>3.16	>3.16	>3.16	>3.16	>3.16
D-87135	S107728			69,0	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
D-87130	S107723		D2: 00/14PH	-1,0	60,5	42,1	73,7	92,3	>3.16	>3.16	>3.16	>3.16	>3.16	>3.16
D-87130	S107723			71,8	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
D-87128	S107722		D2: 00/14PH	38,9	41,4	30,0	62,8	88,0	>3.16	>3.16	>3.16	>3.16	>3.16	>3.16
D-87128	S107722			75,3	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd

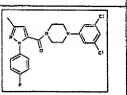
D-No.	Corporate ID	Structure	Patent	KB/HELA	SKOV-3	SF-268	NCI-H460	RKOp27	KB/HELA	SKOV-3	SF-268	NCI-H460	RKOp27	RKOp27 induced
				%INH (3.16ug/ml)					EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]
D-85994	S106490		D2: 00/14PH	27,1	53,2	35,4	77,3	91,3	>3.16	>3.16	>3.16	>3.16	>3.16	>3.16
D-85994	S106490			nd	nd	nd	nd	nd	>3.16	>3.16	>3.16	>3.16	>3.16	>3.16
D-68823	S82663		D2: 00/14PH	10,3	-12,1	nd	nd	nd	nd	nd	nd	nd	nd	nd
D-68780	S82654		D2: 00/14PH	28,3	42,6	nd	nd	nd	nd	nd	nd	nd	nd	nd
D-24203	S28468		D2: 00/14PH	nd	nd	nd	nd	nd	0,029	0,010	0,016	0,022	0,024	>3.16

D-No	Corporate ID	Structure	Patent	KB/HELA	SKOV-3	SF-268	NCI-H460	RKOp27	KB/HELA	SKOV-3	SF-268	NCI-H460	RKOp27	RKOp27 induced
				%INH [3,16ug/ml]					EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]
D-85378	S105825		D3: 00/12PH	39,7	47,0	31,8	77,9	84,2	>3,16	>3,16	>3,16	>3,16	>3,16	>3,16
D-85378	S105825			nd	nd	nd	nd	nd	>3,16	>3,16	>3,16	>3,16	>3,16	>3,16
D-84802	S104160		D3: 00/12PH	72,6	65,4	56,6	84,5	93,0	0,159	0,079	0,144	0,109	0,076	>3,16
D-84802	S104160			nd	nd	nd	nd	nd	0,193	0,099	0,156	0,115	0,076	>3,16
D-84802	S107913			66,1	68,6	50,8	75,0	92,5	0,425	0,137	0,183	0,239	0,156	>3,16
D-83791	S104127		D3: 00/12PH	74,7	57,8	57,9	87,6	97,2	0,124	0,079	0,118	0,227	0,184	>3,16
D-82318	S102229		D3: 00/12PH	84,4	70,3	61,7	90,7	93,5	0,004	0,008	0,004	0,006	0,005	>3,16
D-82318	S107915			66,6	60,8	65,5	81,8	94,3	0,051	0,020	0,022	0,046	0,040	>3,16
D-82318	S107955			92,3	64,5	69,8	89,6	96,6	0,013	0,011	0,016	0,016	0,018	>3,16
D-82318	S107955			nd	nd	nd	nd	nd	0,015	0,012	0,017	0,018	0,018	>3,16

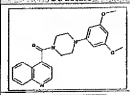
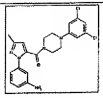
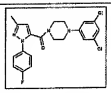
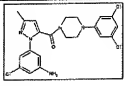
D-No.	Corporate ID	Structure	Patent	KB/HELA	SKOV 3	SF 268	NCI-H460	RKOp27	KB/HELA	SKOV 3	SF 268	NCI H460	RKOp27	RKOp27 induced
				%INH [3.16ug/ml]					EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]
10 (D-86112)	S108869		02/05Z						0,166	0,082	0,094	0,065	0,082	>3,16
12 (D-83326)	S108841		02/05Z						0,060	0,029	0,075	0,064	0,058	>3,16
14 (D-67264)	S131904		02/05Z						0,012	0,006	0,008	0,005	0,006	>3,16
D-87879	S108716		02/05Z	83,6	60,3	76,1	88,4	94,5	0,014	0,006	0,013	0,015	0,010	>3,16
D-87879	S109821			83,5	57,7	64,8	86,9	93,5	0,013	0,006	0,011	0,014	0,013	>3,16
D-87879	S110646			82,8	48,1	71,2	88,4	94,5	0,009	0,006	0,008	0,013	0,012	>3,16

D-No.	Corporate ID	Structure	Patent #	KB/HELA	SKOV-3	SF-268	NCI-H460	RKOp27	KB/HELA	SKOV-3	SF-268	NCI-H460	RKOp27	RKOp27 induced
				%INH [3.16ug/ml]					EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]
D-87914	S109554		02/05Z	78,1	52,4	53,9	86,5	89,4	0,010	0,010	0,012	0,016	0,019	>3,16
D-87914	S127913			82,6	56,3	60,6	84,4	94,2	0,005	0,004	0,010	0,008	0,008	>3,16
D-88961	S111178		02/05Z	nd	nd	nd	nd	nd	0,013	0,016	0,012	0,021	0,020	>3,16
D-105437	S111387		02/05Z	nd	nd	nd	nd	nd	0,012	0,011	0,016	0,018	0,017	>3,16
D-105437	S131815			82,6	59,7	72,5	87,2	84,3	0,019	0,012	0,021	0,016	0,025	>3,16
D-105439	S111389		02/05Z	nd	nd	nd	nd	nd	0,009	0,006	0,006	0,010	0,013	>3,16

D-No.	Corporate ID	Structure	Patent	KB/HELA	SKOV-3	SF-268	NCI-H460	RKOp27	KB/HELA	SKOV-3	SF-268	NCI-H460	RKOp27	RKOp27 induced
				%INH [3,16ug/ml]					EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]	EC50 [µg/mL]
D-105445	S111464		02/05Z	nd	nd	nd	nd	nd	0,005	0,005	0,005	0,009	0,011	>3,16
D-105445	S127997			83,8	65,8	67,8	86,8	96,9	0,057	0,052	0,068	0,070	0,079	>3,16
D-105445	S129112			93,7	63,6	65,0	86,7	93,5	0,005	0,008	0,006	0,017	0,015	>3,16
D-105445	S129363			93,1	63,6	63,9	85,9	93,0	0,008	0,012	0,009	0,017	0,014	>3,16
D-105446	S111470		02/05Z	nd	nd	nd	nd	nd	0,007	0,008	0,009	0,013	0,013	>3,16
D-105446	S127892			84,8	51,7	66,9	86,6	96,5	0,007	0,011	0,014	0,012	0,013	>3,16
D-105446	S129315			94,2	61,3	65,2	83,8	93,4	0,006	0,005	0,005	0,013	0,012	>3,16
D-105446	S129375			94,3	63,9	63,9	85,7	95,0	0,013	0,011	0,010	0,016	0,016	>3,16
D-105446	S130382			86,8	65,9	65,8	82,8	-10,3	0,005	0,007	0,006	0,013	0,013	>3,16
D-105446	S130638			92,9	71,7	69,3	86,2	-13,3	0,010	0,012	0,012	0,016	0,017	>3,16
D-106361	S129846		02/05Z	94,0	66,8	70,6	91,7	99,4	0,015	0,015	0,014	0,017	0,019	>3,16
D-106722	S131580		02/05Z	90,2	59,5	73,8	90,6	95,8	0,015	0,016	0,024	0,019	0,018	>3,16
D-106722	S131580			nd	nd	nd	nd	nd	0,024	0,031	0,028	0,045	0,024	>3,16

D-No.	Corporate ID	Structure	Patent	KB/HELA	SKOV-3	SF-268	NCI-H460	RKOp27	KB/HELA EC50 [µg/mL]	SKOV-3 EC50 [µg/mL]	SF-268 EC50 [µg/mL]	NCI-H460 EC50 [µg/mL]	RKOp27 EC50 [µg/mL]	RKOp27 induced EC50 [µg/mL]
				%INH @16µg/ml										
D-106722	S131580			nd	nd	nd	nd	nd	0,039	0,019	0,051	0,021	0,048	>3,16
D-106722	S131580			nd	nd	nd	nd	nd	0,022	0,020	0,027	0,027	0,018	>3,16
D-105540	S129394		02/05Z	87,3	62,8	68,3	87,4	96,1	0,005	0,008	0,006	0,009	0,010	>3,16

Metabolic stability

D-No.	Structure	Patent	MLM % Remaining after 1h Incubation	RLM % Remaining after 1h Incubation	HLM % Remaining after 1h Incubation	Study
D-24203		D2: 00/14PH	0,0	n.d.	15,0	8311-2002-011 (CEREP)
D-82318		D3: 00/12PH	0,0	1,4	0,3	GPT 02092005
D-105446		02/05Z	n.d.	43,4	82,5	8311-2005-234 (Prolytic) and PRO02076
D-105640		02/05Z	n.d.	21,3	60,2	8311-2005-235 (Prolytic) and PRO02076
D-106361		02/05Z	30,9	n.d.	55,1	PRO02086

MLM: Mouse liver microsomes; RLM: Rat liver microsomes; HLM: human liver microsomes